# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FULLER, Grover, F., Jr.
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950
ETATS-UNIS D'AMERIQUE



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 01.09.2005 |
| Applicant's or agent's file reference: PC26145A | **IMPORTANT NOTIFICATION** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/IB2004/003127 | 27.09.2004 | 08.10.2003 |

Applicant
PFIZER JAPAN, INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

| Name and mailing address of the International preliminary examining authority: | Authorized Officer |
|---|---|
| European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Siefert, A<br>Tel. +49 89 2399-2469 |

Form PCT/IPEA/416 (January 2004)

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference PC26145A | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
|---|---|---|
| International application No. PCT/IB2004/003127 | International filing date *(day/month/year)* 27.09.2004 | Priority date *(day/month/year)* 08.10.2003 |
| International Patent Classification (IPC) or national classification and IPC C07D211/00, C07D401/04 | | |
| Applicant PFIZER JAPAN, INC. et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19.10.2004 | 01.09.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Traegler-Goeldel, M Telephone No. +49 89 2399- |

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-84 as originally filed

   **Claims, Numbers**

   1-14 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-13 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 11-13 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-14 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-14 |
| Industrial applicability (IA) | Yes: | Claims | 1-10, 14 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

re item III:

Claims 11 to 13 have to be considered as being directed to the treatment of the human and/or animal body. Under the terms of Rule 67.1 and Art. 34 (4)a)i) PCT, the International Preliminary Examining Authority is not required to carry out an examination on such claims with respect to industrial applicability.

re item V:

1. Prior art

The Preliminary examination procedure is based on the document cited in the International Search Report:

D1: US-A-5 710 168 (CHENARD BERTRAND L) 20 January 1998 (1998-01-20)
D2: WO 99/21539 A (WARNER LAMBERT CO ; MELTZER LEONARD THEODORE (US)) 6 May 1999 (1999-05-06)
D3: WO 97/23216 A (BIGGE CHRISTOPHER F ; WARNER LAMBERT CO (US); CAI SUI XIONG (US); LAN) 3 July 1997 (1997-07-03)
D4: WO 96/06081 A (BUTLER TODD W ; PFIZER (US); CHENARD BERTRAND L (US) 29 February 1996 (1996-02-29)

2. Novelty

The present 1-[2-(4-hydroxyphenyl)-2-hydroxyethyl]-4-(hetero)arylpiperidin-4-ol derivatives differ from the ones disclosed in D4 by the absence of a methyl or ethyl group in position of the 2-ethanol residue. The present compounds, with the exception of those wherein the 4-hydroxyphenyl residue is substituted by alkoxyalkyl, represent clearly a selection from the from the 2-(hetero)aryl-2-hydroxyethyl-1-piperidine-4-(hetero)aryl-4-ol derivatives according to documents D1 and D2 and from the 4-aryl-4-hydroxy-1-arylalkyl-piperidines as disclosed in D3 showing the same NMDA antagonistic activity. (The main part of) present claim 1 can only be considered to be a novel selection due to the fact that D1 to D3 do not disclose explicitly novelty destroying examples. Thus the subject matter of claims 1 to 14 appears to fulfil the requirements of novelty according to Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Relevant closest prior art for the consideration of inventive step is to be seen in documents D1 to D4, since these documents are concerned with 2-(hetero)aryl-2-hydroxyethyl-1-piperidine-4-(hetero)aryl-4-ol derivatives (D1) and 4-aryl-4-hydroxy-1-arylalkyl-piperidines (D2 to D4) showing at least qualitatively the same NMDA antagonistic activity. The closest prior art for present claim 1 is to be seen in document D1 and D2, since the present compounds with the exception of those wherein the (hetero)aryl substituent may be alkoxyalkyl clearly represent a selection from the 2-(hetero)aryl-2- hydroxyethyl-1-piperidine-4-(hetero)aryl-4-ol derivatives as disclosed in column 3 according to D1 these documents disclose in general and from the the compounds as disclosed in claim 1 according to D2; the present compounds wherein $R^1$ and $R^2$ are hydrogen and $R^3$ is phenyl clearly represent a selection from the 2-(4-hydroxy-phenyl)-2- hydroxyethyl-1-piperidine-4-(phenyl)-4-ol derivatives according to claim 1 of D1.

a, Thus, If the problem underlying the present application were to be seen in provision of further 2-(hetero)aryl-2- hydroxyethyl-1-piperidine-4-(hetero)aryl-4-ol derivatives useful as inhibitors of NMDA receptor sites, the solution of the problem must be considered as being obvious, since this problem has already been solved by documents D1 to D3, from which the present compounds have been selected: the solution of the problem must be considered as being obvious, since the claimed subject matter represents a selection from the compounds generally disclosed according to D1 to D3 used for exactly the same purpose and modified, in order to render the subject matter novel, only by the specific selection of substituents, some of which being already preferred according to D1. Furthermore, in the light of the disclosure of examples 39, 50, 57, 58, 60, 62 and 64 according to D1 all having a 2-hydroxyethyl moiety without substituent in position 1, it was also obvious to replace the methyl or ethyl substituent in position 1 of the 2-hydroxyethyl moiety of compound A acording to D4 by hydrogen.

b, Therefore, the problem underlying the present application, the solution of which could possibly involve an inventive step, is to be seen in the provision of further 2-(hetero)aryl-2- hydroxyethyl-1-piperidine-4-(hetero)aryl-4-ol derivatives useful as inhibitors of NMDA receptor sites, exhibiting a surprising effect compared to the structurally closest compounds of the closest prior art D1 and D2, 1 e.g. better or prolonged activity or a lower toxicity than the compounds of the closest state of the art.

The Applicant's attention is drawn to the fact, that any comparative tests should be made with compounds of the closest prior art, showing the closest possible structural similarity, differing structurally only by the essential feature, i.e. the feature which renders the subject matter novel and which an inventive step may be based on. Only if such an unexpected effect could be demonstrated (preferably by concrete experimental data) an inventive step could be acknowledged. It is brought to the Applicant's attention that any comparison must be representative for the whole scope of the claimed subject matter. Consequently as yet, since no such data are given in the application, the subject matter of present claims 1 to 14 does not fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No problem arises with respect to claims 1 to 10 and 14, since the present compounds may be used for the production of pharmaceutical products.